REMARKS

Claims 1, 3-22 and 31 are pending and stand rejected.

For clarity, applicants have voluntarily amended claim 1 to "...a) performing a genome-wide amplification on genomic DNA...". The basis for this amendment can be found throughout of the application in particular, page 4, second paragraph of the application as filed.

Applicants acknowledge the Examiner's rejection of claims 1, 3, 10-11, 16-17 and 31 under 35 U.S.C. § 102(b) as allegedly being anticipated by Wong et al. (Cancer Research, 1997, vol. 57:2619-2622, hereafter "Wong"). Applicants respectfully traverse these rejections based on the rebuttal arguments of record and presented herein.

Applicants acknowledge the Examiner's rejection of claims 18-22 under 35 U.S.C. § 102(b) as allegedly being anticipated by Adorjan et al. (Nucleic Acids Research, 2002, 30(5)e21, p. 1-9, IDS reference, hereafter "Adrojan"). Applicants have amended claims 18-22 to obviate these rejections.

Applicants acknowledge the Examiner's rejection of claims 1, 4, 8-9, 11, 14-17 and 31 under 35 U.S.C. § 102(a) as allegedly being anticipated by Schatz et al. (Nucleic Acids Research 2004, 32(21):e165, p. 1-7, hereafter "Schatz"). Applicants respectfully traverse these rejections based on provided translation of the claimed priority document.

Applicants acknowledge the Examiner's rejection of claim 12 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Wong in view of Adorjan. Applicants respectfully traverse these rejections based on the rebuttal arguments of record and presented herein.

Applicants acknowledge the Examiner's rejection of claim 13 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Wong in view of Tost et al (Nucleic Acids Research, 2003, 31(9):e50, p. 1-10). Applicants respectfully traverse these rejections based on the rebuttal arguments of record and presented herein.

Applicants acknowledge the Examiner's rejection of claims 5-7 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Schatz in view of Apgar et al. (Human Immunology, 2003, 64(10), Suppl. 1, p. S86, Abstract, hereafter "Apgar"). Applicants respectfully traverse these rejections based on provided translation of the claimed priority document.

Claim 1 interpretation

The subject matter of claim 1 relates to a method for producing DNA for methylation analysis where a) genomic DNA is amplified by means of genome-wide amplification (WGA: whole genome amplification) and then b) using the generated amplificates as a standard in the methylation analysis.

In step a) genomic DNA has been amplified (not pre-treated genomic DNA, for example bisulfite treated genomic DNA or enzymatic treated genomic DNA; see for example page 4 [0006], and examples) via WGA methods to produce non-methylated genomic DNA.

In step b) the generated amplificates are used as <u>standard</u> in the methylation analysis. As the present application discloses on page 3 [0005], it is necessary that the assays for the methylation status analysis are calibrated with fully methylated as well as with non-methylated DNA. At the time of the invention, the prior art for calibration with non-methylated DNA used sperm DNA or artificially produced short non-methylated sequences which are problematic as disclosed on page 4,

first paragraph of the application. It was not known at the time of the invention that the produced genomic DNA by WGA methods can be used as a standard in methods for the detection of 5-methylcytosine.

Rejection under 35 U.S.C. § 102

Novelty over Wong

Claims 1, 3, 10-11, 16-17 and 31 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Wong. Applicants respectfully traverse these rejections.

Wong reports the ability to reduce the amount of DNA necessary for the assay at least 60-fold with PEP and discloses that the extracted DNA samples was modified with bisulfite, amplified with PEP and then amplified with methylation specific primers, and finally, visualized on an agarose gel (p. 2619, right col., 4th paragraph).

Wong does not disclose feature a) of claim 1 of the present invention. Feature a) of claim 1 requires amplification of genomic DNA with WAG methods; it does not require modified genomic DNA. Wong discloses that that DNA samples are first treated with bisulfite and then the modified samples are amplified with PEP (WAG methods). Therefore, Wong does not disclose feature a) of claim 1.

Wong does not disclose feature b) of claim 1 of the present invention where uses the amplificates of the genomic DNA (not treated genomic DNA) as standard for methylation analysis. As mentioned above, Wong uses PEP in order to reduce the amount of DNA necessary for the assay

and not for use as standard. Further, Wong cannot use the PEP amplified DNA samples as standard according to the present invention due to the fact that the amplificates are already modified via bisulfite.

Therefore, the subject matter of claim 1 is novel over Wong. Claims 3, 10-11, 16-17 and 31 depend ultimately from claim 1. Claim 1 is novel over Wong, therefore claims 3, 10-11, 16-17 and 31 are novel over Wong as well.

Novelty over Adorjan

Claims 18-22 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Adorjan. Applicants respectfully traverse these rejections at least based on the current amendments made in claim 18 of the application.

Applicants have amended claim 18 to reflect use of the genomic non-methylated DNA produced according to claim 1 of the invention in a calibration standard mentioned in step a) of claim 18. Support for this amendment can be found throughout of the application, in particular, page 18 [0036].

Adorjan does not disclose use of genomic non-methylated DNA produced according to claim 1 of the present invention. Therefore, the subject matter of claim 1 is novel over Adorjan. Claims 19-22 depend ultimately from claim 18. Claim 18 is novel over Adorjan, therefore claims 19-22 are novel over Adorjan as well.

Novelty over Schatz

Claims 1, 4, 8-9, 11, 14-17 and 31 stand rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Schatz . Applicants respectfully traverse these rejections

Schatz article has been published online on December 2, 2004 after the claimed foreign priority application EP 04090037.5 filed February 05, 2004. Applicants, herewith, submit translation of the aforementioned priority document to obviate this rejection according to 37 CFR 1.55, MPEP § 201.15. Therefore, Applicants, respectfully, request withdrawal of the subject rejection for claims 1, 4, 8-9, 11, 14-17 and 31 based on the provided translation of the claimed priority application.

The submitted translation does not contain contents of Table 1: "Primer for the Multiplex-Amplification" and Table 2: "Oligonucleotides" of the aforementioned claimed priority application, since they show clearly the sequences of the said primers and oligonucleotides. Therefore, translation is not necessary. Further, the Sequence Listings of the said priority documents are not included in the translation due to clarity and being actually in English.

However, if the examiner is of the opinion that translation of the Tables and submission of the Sequence Listings is necessary to overcome the rejections, Applicants reserve the right to provide as such.

Rejection under 35 U.S.C. § 103

Wong in view of Adorjan

Claim 12 stands rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Wong in view of Adorjan. Applicants respectfully traverse this rejection.

As mentioned above, Wong does not disclose amplification of genomic DNA by means of genome-wide amplification. Wong discloses amplification of bisulfite treated and modified DNA by means of PEP (WAG). Bisulfite treated DNA has completely different characteristics and sequences

than untreated genomic DNA. Further, Wong teaches that PEP was used in order to reduce the amount of DNA necessary for the assay.

There is no teaching or suggestion in Wong that genomic DNA was amplified via PEP or any other WAG methods in order to use its amplificates as standards in the methylation analysis. Adorjan fails to cure all the deficiencies of Wong with respect to claim 1. Therefore, it was not obvious for a person skilled in the art to combine the teachings of Wong and Adorjan to arrive at the subject matter of claim 1 of the invention.

Therefore, based at least on its respective dependency from claim 1, claim 12 is patentable over the applied combination of Wong and Adorjan.

Wong in view of Tost

Claim 13 stands rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Wong in view of Tost. Applicants respectfully traverse these rejections.

Again, Wong does not disclose amplification of genomic DNA by means of genome-wide amplification. Wong discloses amplification of bisulfite treated and modified DNA by means of PEP (WAG). Bisulfite treated DNA has completely different characteristics and sequences than untreated genomic DNA. Further, Wong teaches that PEP was used in order to reduce the amount of DNA necessary for the assay.

There is no teaching or suggestion in Wong that genomic DNA was amplified via PEP or any other WAG methods in order to use its amplificates as standards in the methylation analysis. Tost fails to cure all the deficiencies of Wong with respect to claim 1. Therefore, it was not obvious for a person skilled in the art to combine the teachings of Wong and Tost to arrive at the subject matter of claim 1 of the invention.

Therefore, based at least on its respective dependency from claim 1, claim 13 is patentable over the applied combination of Wong and Tost.

Schatz in view of Apgar

Claims 5-7 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Schatz in view of Apgar. Applicants respectfully traverse these rejections.

Based on the provided translation of claimed priority, the subject matter of the invention is patentable over Schatz. Therefore, Applicant respectfully request withdrawal of the subject rejection.

Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request entry of the present Amendment and allowance of the amended claim set provided herein. The Examiner is encouraged to phone Applicants' agent, Ramin Amirsehhi, to resolve any outstanding issues and expedite allowance of this application.

It is believed no fee is due. However, if there are any fees due in connection with filing of this paper that are not accounted for, the Examiner is authorized to charge the fees to our **Deposit Account No. 50-5185**. If a fee is required for an extension of time under 37 C.F.R. 1.136 that is no accounted for already, such an extension of time is requested and the fee should also be charged to our Deposit account.

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